

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/037642

International filing date (day/month/year)
09.11.2004

Priority date (day/month/year)
10.11.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/505, A61K31/519, A61P9/10, A61P19/02, A61P25/16, A61P25/28, A61P37/00, A61P29/00

Applicant
X-CEPTOR THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/037642

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 15-30 (IA)

because:

- ☒ the said international application, or the said claims Nos. 15-30 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 15-30 (IA)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/037642

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	8-11, 14, 20-26, 29-30, 32-36
	No: Claims	1-7, 12, 13, 15-19, 27, 28, 31
Inventive step (IS)	Yes: Claims	
	No: Claims	1-36
Industrial applicability (IA)	Yes: Claims	1-14, 31-36
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Re Item III.

Claims 15-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). However, although not required under the provisions of the PCT, an opinion will be given with respect to novelty and inventive step.

2. Re Item V.

The following documents have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages indicated in the Search Report:

- D1:** WO 02/47690 A (CYTOVIA, INC) 20 June 2002
- D2:** DE 24 44 426 A1 (DELALANDE S.A) 27 March 1975
- D3:** DE 27 29 360 A1 (DELALANDE S.A) 12 January 1978
- D4:** DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YONETOKU, YASUHIRO ET AL: "Preparation of 4-aminopyrimidine derivatives as insulin secretion accelerators" XP002328217. STN Database accession no. 2003:261678
- D5:** WO 2004/032716 A (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 22 April 2004
- D6:** DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAKATANI, TAKAO ET AL: "Preparation of pyrimidine derivatives as drugs for treating disease and disorders of cerebral blood vessels" XP002328218 retrieved from STN Database accession no. 1988:570451
- D7:** WO 02/42280 A (F. HOFFMANN-LA ROCHE AG) 30 May 2002
- D8:** US-A-5 849 758 (KLEEMANN ET AL) 15 December 1998

2.1 Novelty (Art.33(2) PCT)

D1 discloses compounds falling in the definition of claims 1-7,12,13. These compounds are disclosed as activators of caspases. Pharmaceutical compositions comprising these compounds and their use for the treatment of cancer, inflammation, ulcerative colitis, psoriasis are also disclosed. In view of this prior art, the subject matter of claims 1-7,12,13,15-19,27,28,31 is not new.

D2 discloses a number of compounds which fall in the definition of claims 1-7,12,13. Pharmaceutical compositions comprising these compounds, and their use for the treatment of inflammation and cardiocirculatory diseases are also disclosed. This disclosure is prejudicial for the novelty of claims 1-7,12,13,15-19,27.

D3 discloses compounds falling in the definition of claims 1-7,12,13 and their use as medicaments for the treatment of anoxia. This disclosure is prejudicial for the novelty of claims 1-7,12,13.

D4 discloses pharmaceutical compositions comprising compounds falling in the definition of claims 1-7. Their use to accelerate insulin secretion and to treat diabetes and obesity are claimed. This document is prejudicial for the novelty of claims 1-7

2.2 Inventive step (Art.33(3) PCT)

The problem underlying the present application is the provision of medicaments for the treatment of the diseases which are listed in claim 19.

The inventors have found that certain compounds falling in the Markush formula (II) alter the activity of the NGFI-B receptor family. On the base of this discovery, they claim the use of these compounds for the treatment of the aforementioned diseases. In the description, the inventors state that the NGFI-B receptor could be associated with some metabolic pathways which are altered in these diseases. However, the inventor fail to provide any concrete evidence proving that the modulation of this receptor will really provide the desired technical effect (treatment of the disease). Also, from the prior art it is also evident that compounds falling among the claimed ones do not only act on the NGFI-B receptor, but also alter the activity of other receptors and influence other metabolic pathways (see D1, activation of caspases, D4 insulin secretion accelerators). It is therefore not possible in the present case to establish a direct and univocal link between the affinity to the receptor NGFI-B and the diseases to be treated.

Furthermore, the compounds which have been disclosed, and which are shown in figure 1A represent a very narrow selection of the compounds claimed. The comment to Figure 3 at page 12 also seems to indicate that certain compounds according to the invention bind poorly to the target receptors.

For these reasons, the ISA is of the opinion that on the base of the data and the argument provided in the application, it may not be believed that the problem underlying the invention has been solved. In this circumstances the subject matter of the application which is still new may not be considered to involve an inventive step in the sense of Art.33(2) PCT.

2.3 Industrial application (Art.33(4) PCT)

Claims 15-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). The other claims are industrially applicable.

Re Item VI.

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004032716	22 April 2004	8 October 2003	8 October 2002

Re Item VIII.

The terms "lower" alkynyl, or "lower" alkoxy (for example in claim 4, page 89, line 4-5) are not clear.

The wording "diseases modulated by NGFI-B family activity" is also not clear since it is not possible to identify with certainty and univocally which diseases fall into this definition and which do not.